Review Article on Interventional Radiology in Glands

The prostate cancer focal therapy

Filippo Pesapane[1], Francesca Patella[1], Enrico Maria Fumarola[1], Edoardo Zanchetta[1], Chiara Floridi[2], Gianpaolo Carrafiello[3], Chloë Standaert[4]

[1]Postgraduation School in Radiodiagnostics, Università degli Studi di Milano, Milan, Italy; [2]Azienda Ospedaliera Fatebenefratelli e Oftalmico, Milan, Italy; [3]Department of Health Sciences, Diagnostic and Interventional Radiology, San Paolo Hospital, University of Milan, Milan, Italy; [4]Department of Radiology, Ghent University Hospital, Ghent, Belgium

Contributions: (I) Conception and design: F Pesapane, EM Fumarola, F Patella, E Zanchetta, C Standaert; (II) Administrative support: All authors; (III) Provision of study materials or patients: F Pesapane, EM Fumarola, F Patella, E Zanchetta, C Standaert; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: F Pesapane, EM Fumarola, F Patella, E Zanchetta, C Standaert; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Filippo Pesapane. Postgraduation School in Radiodiagnostics, Università degli Studi di Milano, Milan, Italy.
Email: filippopesapane@gmail.com.

Abstract: Despite prostate cancer (PCa) is the leading form of non-cutaneous cancer in men, most patients with PCa die with disease rather than of the disease. Therefore, the risk of overtreatment should be considered by clinicians who have to distinguish between patients with high risk PCa (who would benefit from radical treatment) and patients who may be managed more conservatively, such as through active surveillance or emerging focal therapy (FT). The aim of FT is to eradicate clinically significant disease while protecting key genito-urinary structures and function from injury. While effectiveness studies comparing FT with conventional care options are still lacking, the rationale supporting FT relies on evidence-based advances such as the understanding of the index lesion's central role in the natural history of the PCa and the improvement of multiparametric magnetic resonance imaging (mpMRI) in the detection and risk stratification of PCa. In this literature review, we want to highlight the rationale for FT in PCa management and the current evidence on patient eligibility. Furthermore, we summarize the best imaging modalities to localize the target lesion, describe the current FT techniques in PCa, provide an update on their oncological outcomes and highlight trends for future research.

Keywords: Prostate cancer (PCa); focal therapy (FT); partial ablation; electroporation; interventional radiology

Submitted Sep 02, 2017. Accepted for publication Oct 31, 2017.
doi: 10.21037/gs.2017.11.08
View this article at: http://dx.doi.org/10.21037/gs.2017.11.08

Introduction

Prostate cancer (PCa) is the most common non-cutaneous cancer in western countries (1) with more than one million cases currently diagnosed annually (2). Over the past 25 years, the improvement of treatments, together with the early diagnosis, allowed an increasing from 69% to almost 99% of the 5-year overall survival (OS) for PCa, but these therapies are also associated with considerable morbidity, particularly in genito-urinary dysfunction (1-5).

Therefore, clinicians and patients need to assess together the balance of risks and benefits of therapies using a shared decision-making approach: the aim is to treat the PCa with the lowest risk of recurrence and, at the same time, with minimal morbidity from side effects or complications (6).

The conventional approach includes definitive treatment as the radical prostatectomy (RP) for organ-confined tumor and radiation therapy (RT) for extraprostatic tumor (7). The most important step of patient's management is to differentiate between intra-capsular PCa (stage T1 or T2, according to the TNM staging system) and locally extraglandular PCa (stage T3) (8). Indeed, it was demonstrated that curative treatment is most likely when the TNM stage is ≤ T2c, namely when extracapsular extension (stage T3a), seminal vesicle invasion (stage T3b) or metastatic disease (N+ and/or M+) are not present (8-10).

Advanced PCa is decreasing because of stage migration with prostate-specific antigen (PSA) testing (11). On the other hand, the introduction of PSA-screening, although it has been associated with a significant reduction in PCa mortality, resulted in overdiagnosis and overtreatment of indolent PCa, exposing many men to non-negligible risks and complications without real and concrete benefits (12). For these reasons, conservative treatment option, specifically active surveillance (AS), became increasingly used, demonstrating as a legitimate choice for patients with low risk PCa without any additional morbidity (13). As a result, men with localized PCa face a difficult choice: AS versus RP. The available evidence from contemporary literature demonstrates that there is no relevant difference between AS and RP in 10 years OS (14,15). The patient's dilemma is based on the significant rates of genito-urinary (erectile dysfunction and urinary toxicity, either as obstructive symptoms or incontinence) and rectal side effects of the RP and RT due to their side effects on the adjacent structures (neurovascular bundles, sphincter, bladder neck and rectal wall) (16-19). On the other hand, AS can be associated with psychosocial and financial burdens for participating patients (20). In order to overcome these obstacles and to maintain the oncological benefit of active treatment, while avoiding genito-urinary dysfunction and rectal complications, in the last decade the focal therapy (FT) has been evaluated as a novel strategy in selected patient with localized PCa, representing the middle ground between AS and more aggressive options like RP and RT (21).

FT is a well-established treatment of many other solid-organ malignancies, including those in the breast (22,23), kidney (24,25), thyroid (26), liver (27,28), pancreas (29) and brain (30). The fundamental aspect of FT is the targeted destruction of neoplastic tissue with the preservation of surrounding healthy parenchyma (31). In the case of PCa, this approach allows a more favorable morbidity profile, with the potential for improved urinary and fecal continence and sexual potency outcomes (32,33). Several energy modalities are available and have been used for the purposes of FT: irreversible electroporation (IRE), high-intensity focused ultrasound (HIFU), cryotherapy, focal laser ablation (FLA), photodynamic therapy (PDT), brachytherapy (BT) and radiofrequency ablation (RFA) (34,35).

The approach for PCa FT requires, as the first step, to define a cohort of patients whose PCa features are of higher risk than those indicated for AS and of lower risk than those for RP. These patients should undergo multiparametric magnetic resonance imaging (mpMRI) with the aim to select the target lesion within the prostate, namely the index lesion. The final step is to select types of energy suitable to treat and accomplish an oncological safe organ-sparing ablation with minimal toxicity, based on tumor characteristics and location (21,36-38).

Methods

Using the terms "prostate cancer" or "prostatic neoplasms" and "focal" or "partial" or "targeted" and "ablation" contained in title and/or abstract and/or keywords, a comprehensive literature review was conducted through Medline, Scopus and Google Scholar (from January 1990 to May 2017) databases.

Rationale of PCa FT

PCa has a very long evolution and this involves that patients who receive the diagnosis do not necessarily require therapy: most of PCa patients with low risk of clinically significant disease, neither die prematurely nor have a reduced quality of life (31,39,40). However, although overtreatment of patients with low risk PCa with RP is declining, it still occurs (6).

The use of PSA-screening has led to an impressive increase in the number of clinically insignificant PCa that are being detected and most of them undergo RP: between 2004 and 2007, 58% of men were treated with RP in comparison to less than 10% by AS (6,41). RP can cause loss of erectile function (the most common complication), incontinence and rectal toxic effects such as diarrhea, bleeding, and proctitis (21,34,42). Some physicians argued that for man who need treatment RP is effective and the patient has to accept the side effects (6). However, this same argument formerly used for other cancers (e.g., breast, kidney, liver, pancreas) is now obsolete (22-25,27-29,31,33). Additionally, patients are able to evaluate the benefits of their treatment (6) and nowadays men are not willing to accept any side effect unless they gain years of life expectancy in return (6,43).

Several recent studies have shown that screening for PCa, at worst, are of no benefit in reducing mortality (44) and, at best, prevent the death of 1 man for every 48 men who are treated over a 10-year period (45). On the other hand, there is not yet a definitive way to intercept men who will die from the PCa. Efforts have thus been focused on reducing the considerable burden imposed by complications related to treatment (46) and developing less radical and

invasive therapy to treat men with low or moderate risk for clinically significant PCa. The aim of FT is to treat exclusively tumoral zones and to preserve the remnant gland resulting in lower incidence of side effects and complications compared with radical therapies.

A common criticism of the FT argues that PCa is tipically multifocal with only 15% of men having truly unifocal PCa (47). However, there is now evidence that it is the highest size and grade index lesion that drives the progression to extraglandular extension and metastases (6,48). Moreover, using genomic analysis among 30 men who had died of disseminated PCa, Liu *et al.* found that most metastatic PCa arise from a single precursor cancer cell (49) reinforcing the hypothesis that the natural history of the disease is driven by the index lesion (35,46,50). Risk stratification of the index lesion predicts the outcomes, irrespective of the presence of unilateral or bilateral PCa (51). Thus, FT of the index lesion alone might provide acceptable oncological outcomes because residual PCa in the untreated area does not compromise long-term disease control (31,46).

Selection criteria for FT

FT developed as an alternative way between AS, given the inherent risk of reclassification at subsequent repeat biopsy and due to the cancer-related anxiety, and RP, especially considering the urogenital side effects and complications of treatment (35,42,52). Prospective studies comparing RP to AS demonstrated that patients with low risk PCa are less likely to benefit from treatment than those with high and intermediate risk PCa (35,52). Therefore, FT should be considered as a less aggressive alternative compared with RP in men with significant disease, excluding patients with very low risk PCa eligible for AS (35). The International Task Force of Prostate Cancer outlined the use of FT in selected patients with low risk PCa in 2007 (52). However, further publications highlight the increasing use of FT in men with intermediate risk PCa (39,40). The 2015 international multidisciplinary consensus on inclusion criteria for FT candidates selection for trials included patients with PSA <15 ng/mL, clinical stage ≤ T2a, GS =3+3 or GS= 3+4 (35,37). No tumor volume has been established as a limit for FT (21).

At the best of our knowledge, at least 20 clinical trials on FT in PCa are actively recruiting; 3 of them were recruiting patients with low risk PCa and 17 were recruiting men with low risk or intermediate risk (GS <8) PCa (31). Accordingly, current opinion suggests that suitable candidates for FT can have low or intermediate-risk, with GS >6 PCa localized to one lobe (42) and life expectancy ≥10 years (21). Patients with a single focus of GS =3+4 PCa with limited surrounding tissue of GS =3+3 and patients who are particularly motivated to receive a low-morbidity treatment could be suitable candidates (37), but they should be informed about the lack of long-term follow-up data on the oncological outcome of FT (21).

Detection of the index lesion to be treated

The essential for succesfull FT is the definite identification and localization of the PCa's index lesion (46,48) and mpMRI is actually considered the most accurate imaging technique for clinically significant PCa detection and localization (7,53-55). In order to improve accuracy in detecting PCa, an advanced mpMRI paradigm has been developed in the last decade to obtain both anatomical and functional images (53,56). In 2015, the second version of Prostate Imaging Reporting and Data System (PI-RADSv2) helped to improve the reproducibility in the reading of mpMRI between different centers and radiologists (57), reaching very high sensitivity rate of diagnosis and localization of clinically significant PCa (54,58,59). Both T1-weighted imaging (WI) and T2-WI should be obtained for all prostate mpMRI. T1-WI determines the presence of hemorrhage within the gland (57) and the "T1 hemorrhage exclusion sign" represents an additional aid for localization of larger foci of PCa on mpMRI performed after biopsy (60). On T2W images, PCa appears as hypointense focal lesions; however, this appearance is not specific and can be seen in various conditions such as prostatitis, benign hyperplasia, biopsy-related scars, and after FT (57). Therefore, the diffusion-weighted imaging (DWI) and the apparent diffusion coefficient (ADC) map are the real added-value to this imaging technique since they allow assessment of tissue cellularity: in PCa, the cellularity in the lesion is very high (61), then the lesion appears hypointense on ADC maps and normal tissue appears bright (57). Dynamic contrast-enhanced MRI (DCE-MRI) is a valuable tool in providing a map of blood flow of the prostate, which is increased with more vascular permeability in PCa (62) and it is useful not only for the detection of PCa (63,64), but also when there is suspicion of residual or recurrent disease after RT or FT (65). After FT, mpMRI is used to assess the extent and distribution of the expected necrosis in the target region: on contrast-enhanced T1-WIs, non-

enhancing low-signal-intensity regions are expected at sites of treated PCa (representing necrosis), while focal areas of enhancement (representing viable tissue) are suspicious for recurrence (65). In the last decades, a resurgent interest for functional imaging based on a special theory named intravoxel incoherent motion (IVIM) developed (66) and there are studies demonstrating that extract IVIM parameters in mpMRI is clinically relevant for PCa detection (67-69). One appealing feature of these data is that applying IVIM protocol, the perfusion information could be obtained without the need for intravenous contrast media (68,70,71), which is especially relevant considering nephrogenic systemic fibrosis due to the gadolinium-based contrast (72,73) and the rising concern of gadolinium deposition in neural tissues (74).

Lastly, new imaging fusion platforms allow utilizing functional properties to target candidate lesions for biopsy and FT (75). MRI-guided biopsies of suspicious lesions were shown with increased accuracy compared to conventional blind and random biopsies (13,76). However, some recent studies showed an mpMRI underestimation of the true histological tumor volume and boundaries, which have key implications in planning and performing FT procedures (77). In 2015, Le Nobin *et al.* evaluated the correlation between mpMRI and histopathology for PCa volume and contours estimation using an automatic deformable 3D co-registration platform. They found that histological tumor boundaries tended to be underestimated by mpMRI especially for GS ≥7: for this reason a 9 mm-safety margins around the visible tumor on mpMRI should be applied during FT procedures for effective ablation of the entire PCa (78).

Techniques

IRE

IRE corresponds to a non-thermal ablation modality that uses short electric pulses to create irreversible pores in the cell membrane, thus, causing cell death to the inability to maintain homeostasis (79). IRE uses needle electrodes placed in or around index lesion to deliver a series of brief direct-current electrical pulses with the intention of inducing a permanently porous cell membrane, which result in cell apoptosis (80). Pathology specimens have clarified that IRE lesions cause a complete destruction of tissue extended directly up to the vessel wall, avoiding completely the heat sink effect, a common problem in the thermal ablation techniques. At the same time, IRE lesions show a sharp demarcation between ablated and non-ablated tissue and, if the correct ablation protocols are respected, that can lead to the saving of all the neuro-vascular structures next to the treated area: this characteristic has major implications, particularly in the prostate, where preservation of blood flow is a key component of maintaining erectile function (81).

IRE requires a transperineal approach for electrodes placement and patients need general anesthesia with deep muscle paralysis (82). The number of electrodes used depends on the size and the shape of the index lesion (35). In the design of the IRE protocol the voltages on the electrodes and the distances between the electrodes are chosen in such a way as to produce a range of IRE fields that encompasses the entire undesirable area of tissue. The effects of the electrical pulses are a function of several parameters, including the electrical field, pulse length, pulse shape, interval between pulses and number of pulses. In addition, electrical pulses produce heat, which increases tissue temperature. Damage due to thermal effects is completely different from damage due to IRE. While IRE affects only the cell membrane and does not affect connective tissue, if the temperature during the application of IRE is sufficiently increased to induce thermal damage, it can cause the necrosis of connective tissue, blood vessels or urethra. Therefore, it is desirable when designing an IRE protocol to choose such parameters that, while inducing IRE damage, do not produce thermal modes of damage (83).

The first experience with IRE for Prostate Ablation was of Onik *et al.* in 2007 (81) reaching encouraging results and confirming that IRE lesions in the prostate had unique characteristics compared to thermal lesions. In particular the margins of the IRE lesions were very distinct with a narrow zone of transition from normal to complete necrosis and there was complete destruction within the index nodule and rapid resolution of the post-treatment lesions with marked shrinkage within 2 weeks. After this paper, the attention for this procedure grew and two human *in vivo* pilot studies have been building up with the purpose to determine the safety and the efficacy of IRE in the PCa treatment (84,85). A recent large cohort study by Van den Bos *et al.* (86) confirmed the safety and feasibility of IRE and farther it shows a promising oncological outcome.

However, IRE has also some limitations, as it requires general anesthesia and it is still much more expensive compared to other FT techniques. Given these bounds, it is expected that IRE will be especially useful in treating

tumors otherwise non-treatable by other thermal ablation methods, or when tumors are particularly closed to vital structures as large blood vessels, bowel, nerves and ducts.

HIFU

HIFU was initially used in urology to treat benign prostatic hyperplasia (87). A spherical transducer produces ultrasound waves generated by that deposit energy as they travel through tissues (35). HIFU allows the deposition of a large amount of energy into tissue, resulting in its destruction through cellular disruption and coagulative necrosis in the targeted area while preserving adjacent tissues (88). Efficiency of HIFU depends on acoustic characteristics of targeted tissue and a mathematic model has been developed to be optimized for PCa treatment (89).

Both US-guided probes and MRI-guided systems have been developed in HIFU treatment for PCa. US probes are inserted per rectum and incorporate both imaging and therapeutic transducers in one unit, whereas a prostate-dedicated MRI-HIFU system makes use of either the transrectal or transurethral approach (87). In addition, neoadjuvant transurethral resection of the prostate can be combined with HIFU to reduce the gland size, facilitate tissue destruction and to minimize side effects (90). For some authors, MRI monitoring can be considered superior to US as a guidance tool because it has better anatomical and contrast resolution. Additionally, MRI offers great real-time thermometry, allowing for measurement of temperature changes and cumulative thermal dose, enabling predictions of the tissue damage extension (91).

Cryotherapy

Cryotherapy consists in cellular destruction by freezing: the cellular damages caused vary including direct (membranes disruption) and indirect lesions (ischemia and coagulative necrosis) (92). Cryotherapy was the first ablation technique evaluated as a possible treatment for PCa (93). Cryotherapy is feasible by insertion of dedicated interstitial needles using a transperineal approach under guidance of imaging, usually performed under general anesthesia (35). A nadir temperature of –40 to –50 ℃ is necessary to achieve systematic cell death (35). A rapid freezing followed by a more progressive reheating period provides the best results to induce a "cryolesion" (central necrosis and peripheral edema reaction) with maximal cellular damage (94) whom size may vary according to the type and number of needles, the distance between them, the duration of procedure and the number of freeze-thaw cycles (35). Two freezing cycles are required in the procedure firstly described by Onik *et al.* (95). Needles placement and cryotherapy procedure monitoring are performed under transrectal-US (TRUS) or MRI-real time monitoring (96). Cryotherapy has been extensively used both for whole and partial gland ablation (97), preserving genito-urinary structures and function from injury and suggesting acceptable disease control for both procedures (98).

FLA

FLA's action results from the absorption of radiant energy by tissue receptive chromophores inducing rapid heat production with irreversible damages, resulting in cell death (32). The thermal damage depends on two factors: the amount of heat energy delivered and the depth of light distribution. The first one is determined by both temperature and the heating duration. Studies involving theoretical models have demonstrated that the ideal temperature for prostate FT is generally assumed of 50 ℃ (78,99). Indeed, it has been assessed that, despite immediate protein denaturation could be obtained only for temperatures ≥ 60 ℃, the use of temperature range of 40–60 ℃ could also induce irreversible damages if applied for a longer duration (100). Moreover, the extension of thermal lesions grows with the heating duration. Concerning the depth of light distribution, this depends on the wavelength of the laser. It was reported that wavelengths in the range of 590 to 1,064 nm are the most adequate to induce a maximal photothermic effect in human tissue (101). After FLA, coagulative necrosis develops in 24–72 hours and treated areas appear as well-demarcated foci of necrosis surrounded by a thin rim of hemorrhage with no viable glandular tissue after vital staining (32,102).

FLA is currently considered a minimal invasive treatment, able to reduce the risk of healthy adjacent structures damage (102-104). Since 1993, when Amin *et al.* reported the first case of a clinical application of FLA for local recurrence of PCa (105), a number of studies in the following years have established the feasibility of FLA in PCa treatment (102,106-109). The largest series of patients was evaluated in 2009 by Lindner *et al.* (103) who performed a phase I trial treating 12 patients with biopsy proven low risk PCa with US-guided FLA. The authors concluded that FLA of low risk PCa is feasible and that the targeted region can be ablated with minimal adverse effects, representing an

alternative treatment approach to AS and RP in selected patients (103).

However, some cautions are needed in order to avoid complications. Preoperative thermal damage prediction is required and dedicated software have been developed for the dosimetric planning, allowing the calculation of the light distribution, the temperature rise, and the extent of thermal damage (110). Furthermore, a correct FLA treatment requires the laser-diffusing fiber to be placed within the index lesion (110,111). Some authors assessed that a robot can be successfully used to provide adequate dose coverage of low-volume tumors with difficult location (32). Eventually, FLA requires a perioperative control of the ablated zone. One of the advantages of laser technology is that the control of temperature during the procedure can be performed with MRI: real-time 3D temperature maps could be obtained during FLA procedure and analyzing the acquired images with dedicated software to estimate the thermal changes. This possibility was largely explored in literature both in pre-clinical (112,113) and clinical studies (107-109). In 2017, Natarajan *et al.* (114) proposed to use as an alternative option, the employ of MRI-ultrasound fusion for guidance during FLA. The authors enrolled 11 men with intermediate risk PCa in a prospective pilot study and they used MRI-US fusion to guide laser fibers transrectally into index lesion and thermal probes for real-time monitoring of intraprostatic temperatures during laser activation, demonstrating that this technique appears safe and feasible (114).

PDT

PDT implies the activation of a photosensitive agent (PS) using a source of light with a specific wavelength in the targeted tissue (35). The presence of oxygen is essential since the PDT action is based on the induction of chain reactions leading to the generation of radical intermediates and of the highly cytotoxic singlet oxygen by energy transfer from the photo-excited sensitizer. The latter can induce tissue necrosis either directly with a cytotoxic effect or indirectly causing an acute inflammatory response (35,115,116). Traditional PDT consists in the intravenous injection of a PS which is distributed throughout the body. Then under imaging guidance, standard BT stabilizing frames are placed to allow the positioning in the prostate of small energy-delivering probes that deliver PDT either to a portion of or to the entire gland (117). However, this kind of approach lacks of selectivity and it is linked with some post-treatment inconveniences such as collateral tissue necrosis to adjacent structures or general photosensitivity with consequent need to avoid sunlight exposure for some days after PDT (117). A possible solution is the employ of a variant of PDT called vascular-targeted PDT (VTP) that consists in the use of vascular-activated agents that are currently synthesized from native bacteriochlorophyll, a molecule produced in dark-growing bacteria under aerobic conditions (118). This strategy has some major advantages. Firstly, the radical oxygen species generated by these PS are strictly limited to the vascular bed, determining tissue necrosis only indirectly through vascular occlusion or vascular oxidative stress (119). Secondly, these PS are rapidly cleared first from the circulation and then from the liver. Hence, avoidance of sunlight and other forms of photonic radiation shortly after VTP is not strictly necessary (120). Furthermore, some authors (117,120) suggest that prostate connective tissue is less sensitive to VTP effect and reflects back into the gland a significant amount of the incident light produced during the intervention. The corollary of this theory is that VTP would allow a better preservation of extracapsular structures such as the neurovascular bundle or the adjacent organs. The conclusions of two consecutive clinical trials performed by the Trachtenberg group and other recent studies seem to confirm this fact, although further investigations are needed (121,122). Eventually, the lighting activation is achieved employing near infra-red wavelengths using multichannel diode lasers that deliver illumination from cylindrical laser fibers placed in the prostate under US guidance (123). Also this fact can be considered an advantage, since the use of these wavelengths is associated to a deeper penetration into tissues, as it is convenient for large tissue volume ablations. Because optical characteristics of the prostate are variable, affecting the light absorption and physical effect of PDT and VTP (101), investigators developed dedicated software for the optimization of the parameters of treatment according to tumor and prostate characteristics on preoperative mpMRI (35).

BT

BT is a kind of radiotherapy in which radiation is delivered to the cancer-affected organ by the insertion of seeds containing radioactive material. The biological effect is achieved thanks to the multiple ionizations induced via

the Compton Effect that cause DNA damages, cell cycle arrest and ultimately cell death (35). For PCa, whole-gland BT has become one of the most used options for low and intermediate risk PCa (124). The most utilized radioisotopes are Iodine-125 and Paladium-103.

Two different BT modalities are employed to treat PCa, both performed via a transperineal approach: low-dose rate (LDR), in which radioactive seeds are permanently implanted into the prostate, and high-dose rate (HDR), in which the radiation is delivered by a source temporarily introduced into the prostate tissue, being administered in single or multiple fractions. While LDR-BT is an option for patients with low risk PCa (125), HDR-BT is often used in intermediate or high risk PCa in order to achieve dose escalation (7).

BT, although usually performed on the entire gland tissue, can be easily customized to treat a specific partial prostate volume at a specific dose level, and thus appears to be particularly suitable for FT (126). Considering the higher prevalence of PCa in the peripheral zone, an attractive concept has been to direct BT only to this part of the gland, sparing the anterior base (127). Before this subtotal approach, several groups had performed whole gland treatments with a boosted dose to the index lesion (128). Another technique focuses on the ablation of the half prostate affected by the cancer, with hemi-gland LDR technique (129,130). In 2013, Cosset *et al.* (126) reported on a pilot study in which only index lesions were treated in 21 patients with LDR technique. Although the limited follow-up of that series precluded any definitive data about relapse-free survival, the authors concluded that their approach was feasible and that focal BT, thanks to its ability to treat a well-defined partial prostatic volume with a precise dose, could stand as one of the best FT modalities to be proposed to carefully selected patients.

Traditional whole gland BT uses TRUS to visualize the entire prostate, to calculate its volume for treatment planning and to guide the implantation of radiation sources. In order to treat the specific gland volume affected by the disease, MRI is also widely used for the identification of the suspected area with good results (126,127). MRI-US fusion provides real time guidance to the procedure (124). An invasive localization method is the transperineal mapping biopsy performed via a template grid that is subsequently used for seed implantation (131). Lastly, SPECT images registered with CT has been employed to define intraprostatic biological target volume (132).

RFA

RFA treats tumors by delivering an alternating current, producing ionic agitation, which generates heat (with temperatures of around 100 ℃) thanks to the Joule effect, and eventually cause coagulative necrosis of the target tissue (133). Operatively, the procedure is performed inserting in the body a needle electrode connected to a generator that produces electromagnetic waves with a frequency in the order of 500 kHz (134).

There is limited literature regarding the use of RFA in PCa; however, RFA has proved to be safe and effective in the treatment of primary and secondary hepatic tumors (135) and promising results have been reported in various other neoplasms (136). Prostate RFA is performed with a transperineal approach, using TRUS for needle insertion guidance. A disadvantage of RFA, however, is the inability to precisely assess the extent of the thermal lesion using US, because there are no specific findings correlating with the post-treatment evolution of the index lesion. Therefore, TRUS is not reliable and cannot be used for monitoring the extent of necrosis, which has to be verified by MRI (134). Some technical difficulties need to be considered (137). Monopolar electrodes are susceptible to a cooling effect by adjacent blood vessels that limits the extent of tissue destruction. In addition, using standard monopolar RFA devices, it is difficult to obtain areas of consistent and complete cell-kill with precise margins. Another major obstacle comes from the technical difficulties in using MRI to guide the FT: the RF generator, indeed, may interfere with the radiofrequency pulses of the MR system and the needle electrode produces large image artifacts. Subtotal RFA has been described in cases of recurrent PCa after prior RT showing good results in term of tissue ablation and low complication rate (138). Given the paucity of data, the use of RFA for PCa remains experimental (139) and it is not still mentioned among the "Alternative Local Treatment Options" in the most recent guidelines produced by the competent European societies (7).

Outcomes

Currently, insufficient data are available to evaluate the long-term oncological FT effectiveness in PCa. The studies on FT are small with a large heterogeneity in study design, target population, risk stratification, type of focal ablation, follow-up schedule and outcome measures of morbidity.

Also, the encouraging short-to-midterm outcomes comes from high volume expert centers and reproducibility still has to be confirmed by larger, standardized and controlled studies.

Successful FT consists in effective ablation of the index lesion, improving oncological outcomes and preservation of surrounding structures as assessed by the very low incidence of urinary and sexual disfunctions. Published trials of FT have determined ablation success by using a predetermined protocol of mpMRI of the treatment zone with targeted biopsy as necessary (37).

Oncological success has not been clearly defined, but its evaluation can be derived from the agreed definitions of treatment failure as assessed by PSA monitoring, post-treatment biopsy sampling and rates of retreatment (31). Current literature uses the American Society Radiation oncology (ASTRO) criteria and the Phoenix criteria for the PSA monitoring (127). However, these criteria have not been validated for use with FT, in which considerable amount of functional prostate parenchyma is preserved which continues to produce physiological PSA. Mandatory prostate biopsy one year after treatment is a widely used outcome measure in the available literature and provides a useful tool in assessing the efficacy of FT (40). Other typical triggers for biopsy include rising serum PSA or detection of a suspicious lesion on postoperative mpMRI (37,140). The 2015 expert consensus panel agreed that a residual disease GS ≥3+4 in the treated area represents treatment failure (37). The expert consensus is that retreatment rates of ≤20% after FT are clinically acceptable (37).

As recently described by Valerio *et al.* (39,40), 3,230 patients who underwent FT has been analyzed in 37 clinical studies using different sources of energy; most studies are on focal HIFU (13) and focal cryotherapy (11) whereas focal PDT (3), FLA (4), BT (2), IRE (3) and RFA (1) are less extensively studied. To date, cryotherapy is the most extensively investigated FT strategy (11 series evaluating focal cryotherapy in 1,950 patients): OS and disease-specific survival were 100% and 100% respectively, the biochemical recurrence-free survival was 71–93%, significant residual PCa in the treated area ranged from 0% to 6.5% and the probability of secondary treatment was 3.3–18.6% after 9–70 months of follow-up monitoring. Significant adverse events, in most parts cases of recto-urethral fistula occurred in only 2.5% patients; pad-free continence and erectile function preservation were achieved in 100% and 81.5% respectively (31,40,141). In HIFU strategies, Valerio *et al.* have taken into account 13 series evaluating focal HIFU in 346 men (40). Despite the heterogeneity of the materials, the methods and the population of the studies, the primary results were encouraging, showing a low overall probability of transition to secondary local treatment of 7.8%, an excellent OS and disease-specific survival of 100% and an achievement of 100% in pad-free continence and in erectile function preservation. Significant adverse events occurred in only 1.5% of cases (40).

Clinical data assessing use of PDT in PCa remains limited. In a large series and a pooled analysis of trials, post-treatment recurrent PCa rates were around 25% at biopsy sampling after 6 months and salve RP for locally recurrent PCa has been reported safe and effective (123,142,143). Significant adverse events occurred in 10.6% (40). Early studies have demonstrated the safety and feasibility of FLA but studies are small and outcome data are premature with the presence of significant cancer in the treated area between 2.4–4.8% and secondary treatment in none (40). Only 2 series in 339 patients have reported oncological outcomes of focal BT with a biochemical recurrence-free survival rate at the 5-year follow-up of 92% was reported (127). In another smaller series a 5% residual PCa rate at the treatment site was reported (126,144). IRE has been studied in 141 patients, with significant residual PCa in the treated area between 2.9% and 19% and transition to secondary treatment in 12% (39,80). RFA has been studied in only 1 study in 15 men (134).

FT for PCa enables the neurovascular bundles to be spared, thereby reducing the risk of sexual dysfunction or incontinence. To date, considerable heterogeneity exists in the outcome measures used to define post-treatment sexual function with either the International Index Of Erectile Function (IIEF) or Sexual Healthy Inventory for Men (SHIM) questionnaires being used (31,97,122,126,142). Rates of erectile range from 0% to 42% for cryotherapy (31,145-147), and from 11% to 45% for HIFU (31,148,149). Insufficient data are available to determine rates for the other FT modalities. Barret *et al.* compared three groups of patients undergoing cryotherapy, HIFU, PDT and identified no difference in postoperative IIEF scores between treatment groups (4).

Similar to erectile function, preserved continence after FT for PCa has not been reported universally but seems to do better than in RP: rates of pad-free status are reported to be between 85–100% in cryotherapy (4,31,40,145,148,149), but there is only limited data for the remaining FT modalities. Objective measures including the International Prostate Symptom Score (IPSS) have been

introduced to quantify lower urinary tract symptoms and limited reductions in mean IPSS of 3–8 have been reported after cryotherapy, HIFU and PDT up to 6 months after FT (4,31,102,142,148,149).

No formal data are currently available for assessing cost-effectiveness but as FT progress, cost reductions in equipment and facilities will occur and will correspond with a reduction in cost per patient. Minimally invasive approaches lead to reductions in length of hospital stay and associated inpatient procedures, but patients require more stringent follow-up monitoring with costly imaging modalities and potential retreatments.

Conclusions

FT consists in ablation of the index lesion (31,37,40) in men with low or moderate risk of clinically significant PCa. Although definitive data about long-term cancer control are still lacking, FT represents a valid alternative to the AS, entailing cancer-related anxiety, and RP, whose adverse effects may reduce the patient's quality of life.

With accurate localization of the index lesion, FT can provide uncompromised oncologic outcome with significantly less comorbidity and with genito-urinary functional preservation.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare

References

1. Torre LA, Siegel RL, Ward EM, et al. Global cancer incidence and mortality rates and trends--an update. Cancer Epidemiol Biomarkers Prev 2016;25:16-27.
2. Cooperberg MR, Chan JM. Epidemiology of prostate cancer. World J Urol 2017;35:849.
3. Singh J, Greer PB, White MA, et al. Treatment-related morbidity in prostate cancer: a comparison of 3-dimensional conformal radiation therapy with and without image guidance using implanted fiducial markers. Int J Radiat Oncol Biol Phys 2013;85:1018-23.
4. Barret E, Ahallal Y, Sanchez-Salas R, et al. Morbidity of focal therapy in the treatment of localized prostate cancer. Eur Urol 2013;63:618-22.
5. Bonekamp D, Jacobs MA, El-Khouli R, et al. Advancements in MR imaging of the prostate: from diagnosis to interventions. Radiographics 2011;31:677-703.
6. Bass EJ, Ahmed HU. Focal therapy in prostate cancer: A review of seven common controversies. Cancer Treat Rev 2016;51:27-34.
7. Mottet N, Bellmunt J, Bolla M, et al. EAU-ESTRO-SIOG guidelines on prostate cancer. Part 1: screening, diagnosis, and local treatment with curative intent. Eur Urol 2017;71:618-29.
8. Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. Ann Surg Oncol 2010;17:1471-4.
9. Hoeks CM, Barentsz JO, Hambrock T, et al. Prostate cancer: multiparametric MR imaging for detection, localization, and staging. Radiology 2011;261:46-66.
10. Daneshmand S, Quek ML, Stein JP, et al. Prognosis of patients with lymph node positive prostate cancer following radical prostatectomy: long-term results. J Urol 2004;172:2252-5.
11. Buzzoni C, Auvinen A, Roobol MJ, et al. Metastatic prostate cancer incidence and prostate-specific antigen testing: new insights from the european randomized study of screening for prostate cancer. Eur Urol 2015;68:885-90.
12. Lee DJ, Mallin K, Graves AJ, et al. Recent changes in prostate cancer screening practices and prostate cancer epidemiology. J Urol 2017;198:1230-40.
13. Klotz L, Vesprini D, Sethukavalan P, et al. Long-term follow-up of a large active surveillance cohort of patients with prostate cancer. J Clin Oncol 2015;33:272-7.
14. Hamdy FC, Donovan JL, Lane JA, et al. 10-year outcomes after monitoring, surgery, or radiotherapy for localized prostate cancer. N Engl J Med 2016;375:1415-24.
15. Wilt TJ, Brawer MK, Jones KM, et al. Radical prostatectomy versus observation for localized prostate cancer. N Engl J Med 2012;367:203-13.
16. Ficarra V, Novara G, Rosen RC, et al. Systematic review and meta-analysis of studies reporting urinary continence recovery after robot-assisted radical prostatectomy. Eur Urol 2012;62:405-17.
17. Resnick MJ, Koyama T, Fan KH, et al. Long-term functional outcomes after treatment for localized prostate cancer. N Engl J Med 2013;368:436-45.
18. Sheets NC, Goldin GH, Meyer AM, et al. Intensity-modulated radiation therapy, proton therapy, or conformal

radiation therapy and morbidity and disease control in localized prostate cancer. JAMA 2012;307:1611-20.
19. Langley S, Ahmed HU, Al-Qaisieh B, et al. Report of a consensus meeting on focal low dose rate brachytherapy for prostate cancer. BJU Int 2012;109 Suppl 1:7-16.
20. Weerakoon M, Papa N, Lawrentschuk N, et al. The current use of active surveillance in an Australian cohort of men: a pattern of care analysis from the Victorian Prostate Cancer Registry. BJU Int 2015;115 Suppl 5:50-6.
21. Cathelineau X, Sanchez-Salas R. Focal therapy for prostate cancer: pending questions. Curr Urol Rep 2016;17:86.
22. Page DL, Johnson JE. Controversies in the local management of invasive and non-invasive breast cancer. Cancer Lett 1995;90:91-6.
23. Vaidya JS, Joseph DJ, Tobias JS, et al. Targeted intraoperative radiotherapy versus whole breast radiotherapy for breast cancer (TARGIT-A trial): an international, prospective, randomised, non-inferiority phase 3 trial. Lancet 2010;376:91-102.
24. Lasry JC, Margolese RG. Fear of recurrence, breast-conserving surgery, and the trade-off hypothesis. Cancer 1992;69:2111-5.
25. Mukamel E, Konichezky M, Engelstein D, et al. Incidental small renal tumors accompanying clinically overt renal cell carcinoma. J Urol 1988;140:22-4.
26. Morelli F, Sacrini A, Pompili G, et al. Microwave ablation for thyroid nodules: a new string to the bow for percutaneous treatments? Gland Surg 2016;5:553-8.
27. Lucchina N, Tsetis D, Ierardi AM, et al. Current role of microwave ablation in the treatment of small hepatocellular carcinomas. Ann Gastroenterol 2016;29:460-5.
28. Pesapane F, Nezami N, Patella F, et al. New concepts in embolotherapy of HCC. Med Oncol 2017;34:58.
29. Ierardi AM, Lucchina N, Bacuzzi A, et al. Percutaneous ablation therapies of inoperable pancreatic cancer: a systematic review. Ann Gastroenterol 2015;28:431-9.
30. Tsao MN. Brain metastases: advances over the decades. Ann Palliat Med 2015;4:225-32.
31. Perera M, Krishnananthan N, Lindner U, et al. An update on focal therapy for prostate cancer. Nat Rev Urol 2016;13:641-53.
32. Lindner U, Trachtenberg J, Lawrentschuk N. Focal therapy in prostate cancer: modalities, findings and future considerations. Nat Rev Urol 2010;7:562-71.
33. Ahmed HU, Pendse D, Illing R, et al. Will focal therapy become a standard of care for men with localized prostate cancer? Nat Clin Pract Oncol 2007;4:632-42.
34. Bostwick DG, Waters DJ, Farley ER, et al. Group consensus reports from the Consensus Conference on Focal Treatment of Prostatic Carcinoma, Celebration, Florida, February 24, 2006. Urology 2007;70:42-4.
35. Ouzzane A, Betrouni N, Valerio M, et al. Focal therapy as primary treatment for localized prostate cancer: definition, needs and future. Future Oncol 2017;13:727-41.
36. de la Rosette J, Ahmed H, Barentsz J, et al. Focal therapy in prostate cancer-report from a consensus panel. J Endourol 2010;24:775-80.
37. Donaldson IA, Alonzi R, Barratt D, et al. Focal therapy: patients, interventions, and outcomes--a report from a consensus meeting. Eur Urol 2015;67:771-7.
38. Muller BG, van den Bos W, Pinto PA, et al. Imaging modalities in focal therapy: patient selection, treatment guidance, and follow-up. Curr Opin Urol 2014;24:218-24.
39. Valerio M, Ahmed HU, Emberton M, et al. The role of focal therapy in the management of localised prostate cancer: a systematic review. Eur Urol 2014;66:732-51.
40. Valerio M, Cerantola Y, Eggener SE, et al. New and Established Technology in Focal Ablation of the Prostate: A Systematic Review. Eur Urol 2017;71:17-34.
41. Chamie K, Williams SB, Hershman DL, et al. Population-based assessment of determining predictors for quality of prostate cancer surveillance. Cancer 2015;121:4150-7.
42. Klotz L. Active surveillance, quality of life, and cancer-related anxiety. Eur Urol 2013;64:37-9.
43. King MT, Viney R, Smith DP, et al. Survival gains needed to offset persistent adverse treatment effects in localised prostate cancer. Br J Cancer 2012;106:638-45.
44. Andriole GL, Crawford ED, Grubb RL 3rd, et al. Mortality results from a randomized prostate-cancer screening trial. N Engl J Med 2009;360:1310-9.
45. Schroder FH, Hugosson J, Roobol MJ, et al. Screening and prostate-cancer mortality in a randomized European study. N Engl J Med 2009;360:1320-8.
46. Ahmed HU. The index lesion and the origin of prostate cancer. N Engl J Med 2009;361:1704-6.
47. Masterson TA, Cheng L, Koch MO. Pathological characterization of unifocal prostate cancers in whole-mount radical prostatectomy specimens. BJU Int 2011;107:1587-91.
48. Bott SR, Ahmed HU, Hindley RG, et al. The index lesion and focal therapy: an analysis of the pathological characteristics of prostate cancer. BJU Int 2010;106:1607-11.
49. Liu W, Laitinen S, Khan S, et al. Copy number analysis indicates monoclonal origin of lethal metastatic prostate cancer. Nat Med 2009;15:559-65.

50. Ohori M, Kattan MW, Koh H, et al. Predicting the presence and side of extracapsular extension: a nomogram for staging prostate cancer. J Urol 2004;171:1844-9; discussion 1849.
51. Tareen B, Godoy G, Taneja SS. Focal therapy: a new paradigm for the treatment of prostate cancer. Rev Urol 2009;11:203-12.
52. Eggener SE, Scardino PT, Carroll PR, et al. Focal therapy for localized prostate cancer: a critical appraisal of rationale and modalities. J Urol 2007;178:2260-7.
53. Kurhanewicz J, Vigneron D, Carroll P, et al. Multiparametric magnetic resonance imaging in prostate cancer: present and future. Curr Opin Urol 2008;18:71-7.
54. De Visschere PJ, Briganti A, Futterer JJ, et al. Role of multiparametric magnetic resonance imaging in early detection of prostate cancer. Insights Imaging 2016;7:205-14.
55. Futterer JJ, Briganti A, De Visschere P, et al. Can clinically significant prostate cancer be detected with multiparametric magnetic resonance imaging? A systematic review of the literature. Eur Urol 2015;68:1045-53.
56. Vargas HA, Akin O, Franiel T, et al. Diffusion-weighted endorectal MR imaging at 3 T for prostate cancer: tumor detection and assessment of aggressiveness. Radiology 2011;259:775-84.
57. Weinreb JC, Barentsz JO, Choyke PL, et al. PI-RADS Prostate Imaging - Reporting and Data System: 2015, Version 2. Eur Urol 2016;69:16-40.
58. Lim CS, McInnes MDF, Flood TA, et al. Prostate imaging reporting and data system, version 2, assessment categories and pathologic outcomes in patients with gleason score 3 + 4 = 7 prostate cancer diagnosed at biopsy. AJR Am J Roentgenol 2017;208:1037-44.
59. Lim CS, McInnes MD, Lim RS, et al. Prognostic value of Prostate Imaging and Data Reporting System (PI-RADS) v. 2 assessment categories 4 and 5 compared to histopathological outcomes after radical prostatectomy. J Magn Reson Imaging 2017;46:257-66.
60. Pesapane F, Villeirs G, De Visschere P. The T1 Hemorrhage Exclusion Sign in the Detection of Prostate Cancer at MRI. J Belg Radiol 2017;101:15.
61. Padhani AR, Liu G, Koh DM, et al. Diffusion-weighted magnetic resonance imaging as a cancer biomarker: consensus and recommendations. Neoplasia 2009;11:102-25.
62. Wallace TJ, Torre T, Grob M, et al. Current approaches, challenges and future directions for monitoring treatment response in prostate cancer. J Cancer 2014;5:3-24.
63. Hara N, Okuizumi M, Koike H, et al. Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) is a useful modality for the precise detection and staging of early prostate cancer. Prostate 2005;62:140-7.
64. Alonzo F, Melodelima C, Bratan F, et al. Detection of locally radio-recurrent prostate cancer at multiparametric MRI: Can dynamic contrast-enhanced imaging be omitted? Diagn Interv Imaging 2016;97:433-41.
65. Vargas HA, Wassberg C, Akin O, et al. MR imaging of treated prostate cancer. Radiology 2012;262:26-42.
66. Le Bihan D. Intravoxel incoherent motion perfusion MR imaging: a wake-up call. Radiology 2008;249:748-52.
67. Pang Y, Turkbey B, Bernardo M, et al. Intravoxel incoherent motion MR imaging for prostate cancer: an evaluation of perfusion fraction and diffusion coefficient derived from different b-value combinations. Magn Reson Med 2013;69:553-62.
68. Pesapane F, Patella F, Fumarola EM, et al. Intravoxel incoherent motion (IVIM) diffusion weighted imaging (DWI) in the periferic prostate cancer detection and stratification. Med Oncol 2017;34:35.
69. Valerio M, Zini C, Fierro D, et al. 3T multiparametric MRI of the prostate: Does intravoxel incoherent motion diffusion imaging have a role in the detection and stratification of prostate cancer in the peripheral zone? Eur J Radiol 2016;85:790-4.
70. Le Bihan D, Breton E, Lallemand D, et al. Separation of diffusion and perfusion in intravoxel incoherent motion MR imaging. Radiology 1988;168:497-505.
71. Prince MR, Zhang HL, Roditi GH, et al. Risk factors for NSF: a literature review. J Magn Reson Imaging 2009;30:1298-308.
72. Mithal LB, Patel PS, Mithal D, et al. Use of gadolinium-based magnetic resonance imaging contrast agents and awareness of brain gadolinium deposition among pediatric providers in North America. Pediatr Radiol 2017;47:657-64.
73. Wagner B, Drel V, Gorin Y. Pathophysiology of gadolinium-associated systemic fibrosis. Am J Physiol Renal Physiol 2016;311:F1-11.
74. McDonald RJ, McDonald JS, Kallmes DF, et al. Gadolinium Deposition in Human Brain Tissues after Contrast-enhanced MR Imaging in Adult Patients without Intracranial Abnormalities. Radiology 2017;285:546-54.
75. Tay KJ, Schulman AA, Sze C, et al. New advances in focal therapy for early stage prostate cancer. Expert Rev Anticancer Ther 2017;17:737-43.
76. Ahmed HU, El-Shater Bosaily A, Brown LC, et al.

Diagnostic accuracy of multi-parametric MRI and TRUS biopsy in prostate cancer (PROMIS): a paired validating confirmatory study. Lancet 2017;389:815-22.
77. Cornud F, Khoury G, Bouazza N, et al. Tumor target volume for focal therapy of prostate cancer-does multiparametric magnetic resonance imaging allow for a reliable estimation? J Urol 2014;191:1272-9.
78. van Nimwegen SA, L'Eplattenier HF, Rem AI, et al. Nd:YAG surgical laser effects in canine prostate tissue: temperature and damage distribution. Phys Med Biol 2009;54:29-44.
79. Davalos RV, Mir IL, Rubinsky B. Tissue ablation with irreversible electroporation. Ann Biomed Eng 2005;33:223-31.
80. Ting F, Tran M, Bohm M, et al. Focal irreversible electroporation for prostate cancer: functional outcomes and short-term oncological control. Prostate Cancer Prostatic Dis 2016;19:46-52.
81. Onik G, Mikus P, Rubinsky B. Irreversible electroporation: implications for prostate ablation. Technol Cancer Res Treat 2007;6:295-300.
82. Valerio M, Stricker PD, Ahmed HU, et al. Initial assessment of safety and clinical feasibility of irreversible electroporation in the focal treatment of prostate cancer. Prostate Cancer Prostatic Dis 2014;17:343-7.
83. Rubinsky J, Onik G, Mikus P, et al. Optimal parameters for the destruction of prostate cancer using irreversible electroporation. J Urol 2008;180:2668-74.
84. van den Bos W, de Bruin DM, Muller BG, et al. The safety and efficacy of irreversible electroporation for the ablation of prostate cancer: a multicentre prospective human in vivo pilot study protocol. BMJ Open 2014;4:e006382.
85. Valerio M, Dickinson L, Ali A, et al. A prospective development study investigating focal irreversible electroporation in men with localised prostate cancer: Nanoknife Electroporation Ablation Trial (NEAT). Contemp Clin Trials 2014;39:57-65.
86. van den Bos W, Scheltema MJ, Siriwardana AR, et al. Focal irreversible electroporation as primary treatment for localized prostate cancer. BJU Int 2017. [Epub ahead of print].
87. She WH, Cheung TT, Jenkins CR, et al. Clinical applications of high-intensity focused ultrasound. Hong Kong Med J 2016;22:382-92.
88. Beerlage HP, Thuroff S, Debruyne FM, et al. Transrectal high-intensity focused ultrasound using the Ablatherm device in the treatment of localized prostate carcinoma. Urology 1999;54:273-7.
89. Chavrier F, Chapelon JY, Gelet A, et al. Modeling of high-intensity focused ultrasound-induced lesions in the presence of cavitation bubbles. J Acoust Soc Am 2000;108:432-40.
90. Chaussy CG, Thuroff S. High-intensity focused ultrasound for the treatment of prostate cancer: a review. J Endourol 2017;31:S30-7.
91. Copelan A, Hartman J, Chehab M, et al. High-intensity focused ultrasound: current status for image-guided therapy. Semin Intervent Radiol 2015;32:398-415.
92. Hoffmann NE, Bischof JC. The cryobiology of cryosurgical injury. Urology 2002;60:40-9.
93. Gonder MJ, Soanes WA, Shulman S. Cryosurgical treatment of the prostate. Invest Urol 1966;3:372-8.
94. Cazzato RL, Garnon J, Ramamurthy N, et al. Percutaneous image-guided cryoablation: current applications and results in the oncologic field. Med Oncol 2016;33:140.
95. Onik GM, Cohen JK, Reyes GD, et al. Transrectal ultrasound-guided percutaneous radical cryosurgical ablation of the prostate. Cancer 1993;72:1291-9.
96. Gangi A, Tsoumakidou G, Abdelli O, et al. Percutaneous MR-guided cryoablation of prostate cancer: initial experience. Eur Radiol 2012;22:1829-35.
97. Barqawi AB, Stoimenova D, Krughoff K, et al. Targeted focal therapy for the management of organ confined prostate cancer. J Urol 2014;192:749-53.
98. Gao L, Yang L, Qian S, et al. Cryosurgery would be an effective option for clinically localized prostate cancer: a meta-analysis and systematic review. Sci Rep 2016;6:27490.
99. Bhowmick S, Swanlund DJ, Coad JE, et al. Evaluation of thermal therapy in a prostate cancer model using a wet electrode radiofrequency probe. J Endourol 2001;15:629-40.
100. Ritchie KP, Keller BM, Syed KM, et al. Hyperthermia (heat shock)-induced protein denaturation in liver, muscle and lens tissue as determined by differential scanning calorimetry. Int J Hyperthermia 1994;10:605-18.
101. Jankun J, Keck RW, Skrzypczak-Jankun E, et al. Diverse optical characteristic of the prostate and light delivery system: implications for computer modelling of prostatic photodynamic therapy. BJU Int 2005;95:1237-44.
102. Lindner U, Lawrentschuk N, Weersink RA, et al. Focal laser ablation for prostate cancer followed by radical prostatectomy: validation of focal therapy and imaging accuracy. Eur Urol 2010;57:1111-4.
103. Lindner U, Weersink RA, Haider MA, et al. Image guided photothermal focal therapy for localized prostate cancer:

phase I trial. J Urol 2009;182:1371-7.
104. Colin P, Nevoux P, Marqa M, et al. Focal laser interstitial thermotherapy (LITT) at 980 nm for prostate cancer: treatment feasibility in Dunning R3327-AT2 rat prostate tumour. BJU Int 2012;109:452-8.
105. Amin Z, Lees WR, Bown SG. Technical note: interstitial laser photocoagulation for the treatment of prostatic cancer. Br J Radiol 1993;66:1044-7.
106. Atri M, Gertner MR, Haider MA, et al. Contrast-enhanced ultrasonography for real-time monitoring of interstitial laser thermal therapy in the focal treatment of prostate cancer. Can Urol Assoc J 2009;3:125-30.
107. Raz O, Haider MA, Davidson SR, et al. Corrigendum to "Real-Time Magnetic Resonance Imaging-Guided Focal Laser Therapy in Patients with Low-Risk Prostate Cancer" [Eur Urol 2010;58:173-77]. Eur Urol 2010;58:473.
108. Raz O, Haider MA, Davidson SR, et al. Real-time magnetic resonance imaging-guided focal laser therapy in patients with low-risk prostate cancer. Eur Urol 2010;58:173-7.
109. Woodrum DA, Mynderse LA, Gorny KR, et al. 3.0T MR-guided laser ablation of a prostate cancer recurrence in the postsurgical prostate bed. J Vasc Interv Radiol 2011;22:929-34.
110. Marqa MF, Colin P, Nevoux P, et al. Focal laser ablation of prostate cancer: numerical simulation of temperature and damage distribution. Biomed Eng Online 2011;10:45.
111. Colin P, Mordon S, Nevoux P, et al. Focal laser ablation of prostate cancer: definition, needs, and future. Adv Urol 2012;2012:589160.
112. Stafford RJ, Shetty A, Elliott AM, et al. Magnetic resonance guided, focal laser induced interstitial thermal therapy in a canine prostate model. J Urol 2010;184:1514-20.
113. Peters RD, Chan E, Trachtenberg J, et al. Magnetic resonance thermometry for predicting thermal damage: an application of interstitial laser coagulation in an in vivo canine prostate model. Magn Reson Med 2000;44:873-83.
114. Natarajan S, Jones TA, Priester AM, et al. Focal laser ablation of prostate cancer: feasibility of magnetic resonance imaging/ultrasound fusion for guidance. J Urol 2017;198:839-47.
115. Dougherty TJ. Photodynamic therapy. Photochem Photobiol 1993;58:895-900.
116. Bozzini G, Colin P, Betrouni N, et al. Photodynamic therapy in urology: what can we do now and where are we heading? Photodiagnosis Photodyn Ther 2012;9:261-73.
117. Lepor H. Vascular targeted photodynamic therapy for localized prostate cancer. Rev Urol 2008;10:254-61.
118. Schreiber S, Gross S, Brandis A, et al. Local photodynamic therapy (PDT) of rat C6 glioma xenografts with Pd-bacteriopheophorbide leads to decreased metastases and increase of animal cure compared with surgery. Int J Cancer 2002;99:279-85.
119. Berdugo M, Bejjani RA, Valamanesh F, et al. Evaluation of the new photosensitizer Stakel (WST-11) for photodynamic choroidal vessel occlusion in rabbit and rat eyes. Invest Ophthalmol Vis Sci 2008;49:1633-44.
120. Borle F, Radu A, Monnier P, et al. Evaluation of the photosensitizer Tookad for photodynamic therapy on the Syrian golden hamster cheek pouch model: light dose, drug dose and drug-light interval effects. Photochem Photobiol 2003;78:377-83.
121. Trachtenberg J, Weersink RA, Davidson SR, et al. Vascular-targeted photodynamic therapy (padoporfin, WST09) for recurrent prostate cancer after failure of external beam radiotherapy: a study of escalating light doses. BJU Int 2008;102:556-62.
122. Moore CM, Azzouzi AR, Barret E, et al. Determination of optimal drug dose and light dose index to achieve minimally invasive focal ablation of localised prostate cancer using WST11-vascular-targeted photodynamic (VTP) therapy. BJU Int 2015;116:888-96.
123. Azzouzi AR, Barret E, Moore CM, et al. TOOKAD((R)) Soluble vascular-targeted photodynamic (VTP) therapy: determination of optimal treatment conditions and assessment of effects in patients with localised prostate cancer. BJU Int 2013;112:766-74.
124. Peach MS, Trifiletti DM, Libby B. Systematic review of focal prostate brachytherapy and the future implementation of image-guided prostate hdr brachytherapy using MR-Ultrasound Fusion. Prostate Cancer 2016;2016:4754031.
125. Ash D, Flynn A, Battermann J, et al. ESTRO/EAU/EORTC recommendations on permanent seed implantation for localized prostate cancer. Radiother Oncol 2000;57:315-21.
126. Cosset JM, Cathelineau X, Wakil G, et al. Focal brachytherapy for selected low-risk prostate cancers: a pilot study. Brachytherapy 2013;12:331-7.
127. Nguyen PL, Chen MH, Zhang Y, et al. Updated results of magnetic resonance imaging guided partial prostate brachytherapy for favorable risk prostate cancer: implications for focal therapy. J Urol 2012;188:1151-6.
128. Bauman G, Haider M, Van der Heide UA, et al. Boosting imaging defined dominant prostatic tumors: a systematic review. Radiother Oncol 2013;107:274-81.

129. Fernandez Ots A, Bucci J, Chin YS, et al. Hemiablative Focal Low Dose Rate Brachytherapy: A Phase II Trial Protocol. JMIR Res Protoc 2016;5:e98.
130. Laing R, Franklin A, Uribe J, et al. Hemi-gland focal low dose rate prostate brachytherapy: An analysis of dosimetric outcomes. Radiother Oncol 2016;121:310-5.
131. Mahdavi SS, Spadinger IT, Salcudean SE, et al. Focal application of low-dose-rate brachytherapy for prostate cancer: a pilot study. J Contemp Brachytherapy 2017;9:197-208.
132. Ellis RJ, Zhou H, Kim EY, et al. Biochemical disease-free survival rates following definitive low-dose-rate prostate brachytherapy with dose escalation to biologic target volumes identified with SPECT/CT capromab pendetide. Brachytherapy 2007;6:16-25.
133. Hu B, Hu B, Chen L, et al. Contrast-enhanced ultrasonography evaluation of radiofrequency ablation of the prostate: a canine model. J Endourol 2010;24:89-93.
134. Zlotta AR, Djavan B, Matos C, et al. Percutaneous transperineal radiofrequency ablation of prostate tumour: safety, feasibility and pathological effects on human prostate cancer. Br J Urol 1998;81:265-75.
135. Curley SA, Izzo F. Radiofrequency ablation of hepatocellular carcinoma. Minerva Chir 2002;57:165-76.
136. Neeman Z, Wood BJ. Radiofrequency ablation beyond the liver. Tech Vasc Interv Radiol 2002;5:156-63.
137. Richstone L, Ziegelbaum M, Okeke Z, et al. Ablation of bull prostate using novel bipolar radiofrequency ablation probe. J Endourol 2009;23:11-6.
138. Shariat SF, Raptidis G, Masatoschi M, et al. Pilot study of radiofrequency interstitial tumor ablation (RITA) for the treatment of radio-recurrent prostate cancer. Prostate 2005;65:260-7.
139. Magnuson WJ, Mahal A, Yu JB. Emerging Technologies and Techniques in Radiation Therapy. Semin Radiat Oncol 2017;27:34-42.
140. Postema AW, De Reijke TM, Ukimura O, et al. Standardization of definitions in focal therapy of prostate cancer: report from a Delphi consensus project. World J Urol 2016;34:1373-82.
141. Shah TT, Ahmed H, Kanthabalan A, et al. Focal cryotherapy of localized prostate cancer: a systematic review of the literature. Expert Rev Anticancer Ther 2014;14:1337-47.
142. Azzouzi AR, Barret E, Bennet J, et al. TOOKAD(R) Soluble focal therapy: pooled analysis of three phase II studies assessing the minimally invasive ablation of localized prostate cancer. World J Urol 2015;33:945-53.
143. Lebdai S, Villers A, Barret E, et al. Feasibility, safety, and efficacy of salvage radical prostatectomy after Tookad(R) Soluble focal treatment for localized prostate cancer. World J Urol 2015;33:965-71.
144. Cosset JM, Hannoun-Levi JM, Peiffert D, et al. Permanent implant prostate cancer brachytherapy: 2013 state-of-the art. Cancer Radiother 2013;17:111-7.
145. Ward JF, Jones JS. Focal cryotherapy for localized prostate cancer: a report from the national Cryo On-Line Database (COLD) Registry. BJU Int 2012;109:1648-54.
146. Cho S, Kang SH. Current status of cryotherapy for prostate and kidney cancer. Korean J Urol 2014;55:780-8.
147. Onik G, Vaughan D, Lotenfoe R, et al. The "male lumpectomy": focal therapy for prostate cancer using cryoablation results in 48 patients with at least 2-year follow-up. Urol Oncol 2008;26:500-5.
148. Ahmed HU, Freeman A, Kirkham A, et al. Focal therapy for localized prostate cancer: a phase I/II trial. J Urol 2011;185:1246-54.
149. Dickinson L, Ahmed HU, Kirkham AP, et al. A multi-centre prospective development study evaluating focal therapy using high intensity focused ultrasound for localised prostate cancer: The INDEX study. Contemp Clin Trials 2013;36:68-80.

Cite this article as: Pesapane F, Patella F, Fumarola EM, Zanchetta E, Floridi C, Carrafiello G, Standaert C. The prostate cancer focal therapy. Gland Surg 2018;7(2):89-102. doi: 10.21037/gs.2017.11.08

